Bleeding Risk in Patients with Underlying Chronic Kidney Disease Admitted for Acute Coronary Syndromes

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Abstract

A retrospective review of 200 patients with acute coronary syndrome (ACS) and chronic kidney disease (CKD) was compared to 200 patients without CKD to investigate the incidence of bleeding. Logistic regression analysis identified CKD as an independent risk factor for bleeding (OR 1.82, 95% CI 1.02 - 3.25). CKD patients with ACS appear to have more bleeding complications.

Introduction

There are approximately 300,000 people with end stage renal disease (ESRD) and 2 million with chronic kidney disease (CKD) in the United States.[1] Forty-one percent of patients with ESRD will succumb to cardiovascular disease[1] and more than one in five of these deaths will be as a result of an acute myocardial infarction.[2] The inferior outcomes of patients with end stage renal disease following myocardial infarctions have been attributed to a variety of causes including higher prevalence of comorbidities in patients with renal disease, certain vascular characteristics, higher levels of homocysteine and differences in management.[3,4,5] These differences in management include less frequent beta-blocker or aspirin therapy, less utilization of thrombolytics and infrequent percutaneous revascularization procedures in patients with acute myocardial infarctions and CKD compared to patients with normal kidney function.[6,7,8,9]

Medical therapy for acute coronary syndromes (ACS) heavily relies on anticoagulant and antiplatelet therapy.[10] However, due to fear of bleeding complications secondary to uremic platelet dysfunction, patients with CKD commonly do not receive these blood thinning agents, although differences in bleeding complications in patients presenting with ACS with or without CKD have never been evaluated outside a post-hoc analysis of a randomized controlled trial.[11,12]

Thus, the goal of our study was to evaluate the incidence of bleeding complications in patients admitted with ACS and CKD.

Methods

After approval by the appropriate institutional review boards, an analysis of computerized discharge diagnosis was performed at two major hospitals in Honolulu, Hawaii, from January 2000 until June 2003. Patients carrying an ICD9 code for acute coronary syndrome and chronic kidney disease as primary or secondary diagnosis were included. Patients with a creatinine of less then 1.5 mg/dl on admission were excluded from the analysis. The second group of patients with acute coronary syndromes without CKD was identified during the same period of time. In both groups, patients with acute renal failure were excluded from analysis.

Demographic and clinical data were extracted as specified in the results section. Bleeding was defined as either minor or major bleeding episode following the TIMI-bleeding criteria.[13] We categorized participants into two groups based on the existence of chronic kidney disease. Normally distributed data is reported as mean and standard deviation (SD). Characteristics between the two groups were compared by Chi-Square for dichotomous variables and Mann-Whitney U Test and Student's T-test for continuous variables. To determine the independent association between incidence of bleeding and other cofactors including CKD we used binary logistic regression analysis to calculate odds ratios. Alpha-level was set at 0.05, unless otherwise stated. Statistical analyses were performed with the use of SPSS version 10.0 (Chicago, IL).

Results

Baseline Characteristics

We identified 200 patients with and 200 patients without CKD admitted for ACS. Patients with ckd were older then those without CKD (69 ± 13.3 vs 66.5 ± 13.7 years, p=0.079) (Table 1). Patients in the CKD were more likely to be female and non-Caucasian, and had more diabetes, hypertension, previous history of myocardial infarction, cerebral vascular disease,

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peripheral vascular disease, congestive heart failure, and atrial fibrillation (Table 2). On admission, patients with CKD more commonly presented with acute heart failure, more frequently were anemic and had a higher activated partial thromboplastin time (PTT) compared to patients without CKD (Tables 1 and 3).

Incidence of Bleeding

There was a trend towards more clinically overt bleeding in patients with CKD than in patients with normal kidney function (27.5% vs 20.5%, p=0.101) (Table 4). Patients with CKD more frequently received blood transfusions compared to patients admitted with ACS without coexisting renal disease (mean 1.3 ± 3.03 vs 0.83 ± 2.98, p=0.118).

In binary logistic analysis CKD was associated with the occurrence of any kind of bleeding complication (OR 1.82, 95% CI 1.02 to 3.25, p=0.042), as was coronary angiography (OR 3.44, 95% CI 1.87 to 6.34, p<0.0001) after exclusion of patients who underwent coronary artery bypass grafting (Figure 3). Use of Clopidogrel (OR 0.39, 95% CI 0.22 to 0.69) and higher platelet counts (OR 0.98, 95% CI 0.98 to 0.99) were associated with less frequent bleeding.

Therapeutic Interventions

Aspirin, Clopidogrel, GPIIbIIIa-Inhibitors, Enoxaparin, and IV heparin were less frequently administered to CKD patients (Figure 1). Patients with CKD also did not receive as much invasive therapy, with less frequent utilization of diagnostic angiography procedures and percutaneous coronary interventions (Figure 2).

Discussion

This study suggests that patients with chronic renal failure are more at risk for bleeding than those without chronic renal failure. Although we documented a higher incidence of bleeding (27.5% vs 20.5%), and more frequent transfusions in the CKD patients, this was not found to be statistically significant (p=0.101). In logistic regression analysis, after accounting for anti-platelet agents, aspirin, age, and other confounding factors, we found that CKD was associated with the combined outcome of major and minor bleeding, independent of the severity of renal dysfunction. The conflicting results are likely a result of the small number of patients in our initial analysis and this is one of the limitations of our study.

Although one might expect lower bleeding rates with less anti-coagulant therapy,[14,15,16,17] we saw a higher incidence of bleeding. This may be secondary to uremic platelet dysfunction and other, as yet unspecified factors.

All types of anti-coagulation and therapeutic interventions were documented as less frequently employed in CKD patients. It is likely that the pre-

Table 1.— Baseline Characteristics

	CKD (n=200)'	Non-CKD (n=200)	P-value
Age	69 ± 13.3	66.5 ± 13.7	0.079
Female	48%	29%	<0.0001
Ethnicity			0.004
Asian	58%	44.5%	
Pacific Islander	24%	13%	
Caucasian	16%	34%	
Other	2%	8.5%	
Medicare Insurance	70%	32%	<0.0001
Killip Class*			0.0002
Class I	58%	85%	
Class II	36%	7%	
Class III	20%	2%	
Class IV	7%	1%	

* demonstrating no evidence of heart failure in Class I, mild-mod CHF in Class II, overt pulmonary edema in Class III and cardiogenic shock in Class IV (21)

Table 2.— Comorbid conditions

	CKD (n=200)'	Non-CKD (n=200)	P-value
DM‡ using insulin	28%	8%	<0.0001
DM‡ not using insulin	19%	16%	0.372
Hypertension ^	88%	63%	<0.0001
Hyperlipidemia "	40%	42%	0.729
AMI	41%	14%	<0.0001
CVA	23%	6%	<0.0001
PVD	14%	2%	<0.0001
CHF	37%	3.5%	<0.0001
Afib	15%	4.5%	<0.0001

' CKD defined as a Creatinine of ≥1.5 mg/dl

‡ Defined as history of diabetes, regardless of duration of disease, need for antidiabetic agents, or a fasting blood sugar >7 mmol/l or 126 mg/dl

^ Defined as BP > 140/90 on 2 separate occasions

" Dyslipidemia diagnosed by a physician with total cholesterol >200mg/dl, LDL≥ 130, or ≥100 with known coronary artery disease, or HDL less than 40

Table 3.— Baseline Laboratory Values

	CKD' (n=200)	Non-CKD (n=200)	P-value
Hematocrit	35	42	<0.0001
Platelets	233	243	0.283
PTT	39.8	33.5	0.002
INR	1.4	1.2	0.074

' CKD defined as a Creatinine of ≥1.5 mg/dl

Table 4.— Bleeding Complications			
	CKD' (n=200)	Non-CKD (n=200)	P-value
% with documented bleeding	27.5	20.5	0.101
# of PRBC's transfused (SD)	1.3 (3.03)	0.83 (2.98)	0.118

' CKD defined as a Creatinine of ≥1.5 mg/dl

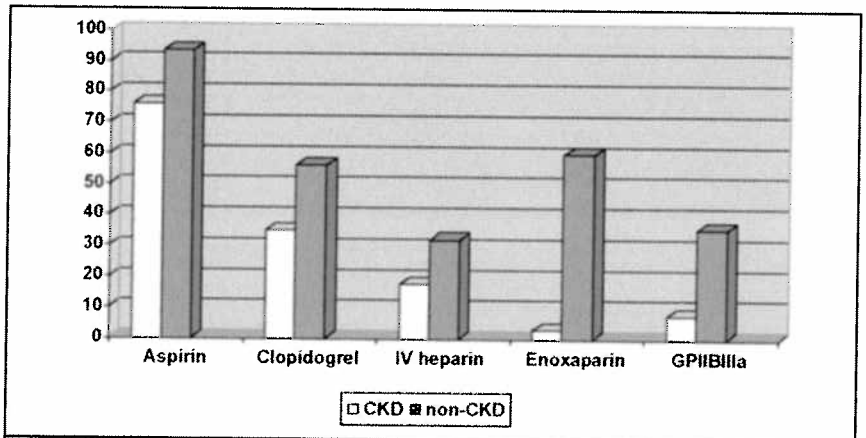

Figure 1.— Anticoagulant Therapy Used in Patients Admitted for Acute Coronary Syndrome

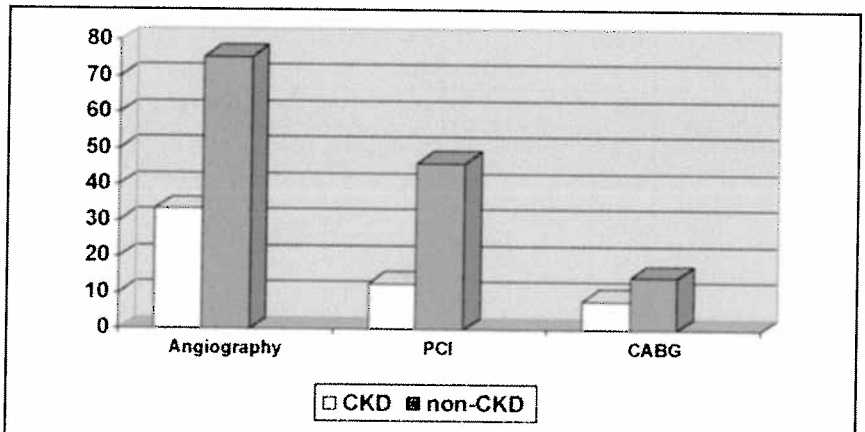

Figure 2.— Invasive Treatments Utilized in Management of Acute Coronary Syndrome Patients

sumed risk of bleeding complications in this group is what motivated the lack of medical interventions. However, this has never been adequately researched as CKD patients are frequently excluded from studies on anti-coagulant therapy. There are no guidelines for the use of GPIIb/IIIa inhibitors in patients with CKD and only recently has dosing information of low-molecular weight heparin in CKD patients been released. Recent studies demonstrate mixed results on the use of anti-coagulant therapy in this group. Two studies utilizing the GPIIb/IIIa inhibitor, abciximab in patients with CKD during PCI fail to demonstrate an increased risk of major bleeding.[11,18] In the ESPRIT trial sub-group analysis, which examined the effects of the GPIIb/IIIa inhibitor eptifibatide in patients with chronic kidney disease undergoing coronary artery stent placement, patients with CKD were found to be more at risk for bleeding.[11] However, in these studies there are limitations that prevent the application of these results to a large number of patients, including small sample sizes, problems with post-hoc analysis and lack of generalizability of the study populations. Freeman's study on the use of GPIIb/IIIa inhibitors in CKD patients presenting with ACS found a two-fold increase in major bleeding events that appeared to correlate with decreasing creatinine clearance.[16] The implications of his findings of increased bleeding, which are similar to those here are unclear, as he also notes that the use of GPIIb/IIIa inhibitors offered a significant protective effect in decreased mortality. Our observation of increased bleeding events in patients with CKD signifies the need for further prospective trials to clarify the risk of bleeding in patients with CKD being treated for ACS.

In addition to uremic platelet dysfunction, the observation of increased bleeding in patients with CKD treated with anticoagulants may be explained by alteration of the pharmacokinetics of anticoagulants in renal insufficiency. The pharmacokinetics of GPIIb/IIIa inhibitors and low molecular weight heparins are altered in those with renal insufficiency.[19,20] It is possible that inadequate dose adjustment may partially account for the increased association with bleeding in those patients in whom they were utilized. In the future, optimal dosing of anticoagulants following acute coronary syndrome in the setting of renal failure needs to be determined.

Our study population was ethnically diverse, with Caucasians accounting for only a minority of the patients examined as compared to other studies, which have been done largely on Caucasian and African-American populations. It is unclear what effect ethnic background may have had on our data.

The design of the study as a retrospective chart review is also limiting in that we can only note associations. In order to really establish whether there is a significant role for uremia in bleeding, we would

need to have a prospective trial. It also hinders us in our evaluation of long-term consequences for bleeding.

Conclusions

Patients with chronic kidney disease routinely receive less anticoagulant and anti-platelet treatment for acute coronary syndrome partly out of concern for bleeding complications. Given that CKD might be a risk factor for bleeding complications, appropriate management strategies must be investigated. Randomized controlled trials are needed to establish the role of uremic platelet dysfunction in bleeding complications and to determine the safety of anti-platelet and anti-coagulant medications.

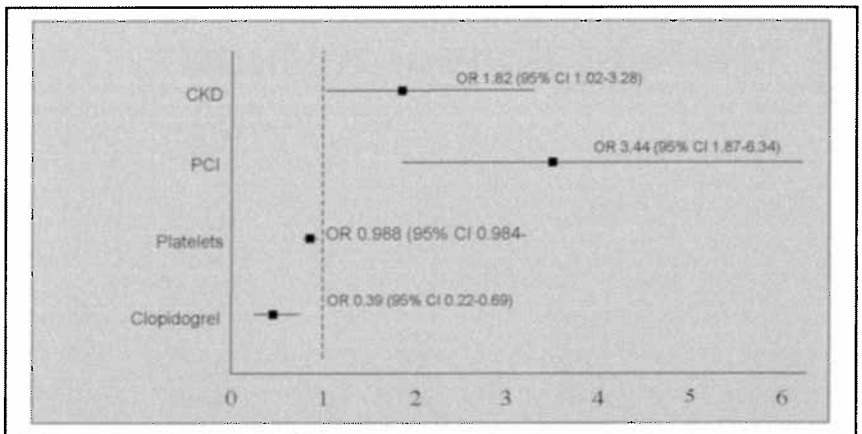

Figure 3.— Logistic Regression Analysis of Bleeding Incidence

Confounders entered in logistic regression model: Aspirin, Plavix, GP2B3A, Enoxaparin, Heparin, age, duration kidney disease, coumadin prior to admission, any cath done, INR max, PTT max, PCI done.

CKD defined as a Creatinine of ≥1.5 mg/dl, PCI is percutaneous intervention, CI confidence interval. Data is plotted as odds ratio with error bars showing 95% confidence interval. Error bars to the right side of the dashed line favor association, those to the left, favor no association.

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